Chapter 4

The catalytic asymmetric 1,4-addition of dialkylzinc reagents to 2-cyclohexenone and unsaturated lactones

4.1 Introduction

In chapter 2 an extensive review was presented on the catalytic asymmetric 1,4-addition reaction has developed by different research groups. The common features in all these catalytic systems are the use of dialkylzinc reagents, toluene or CH_2Cl_2 as solvents, reaction temperatures between –20 and –30°C and $Cu(OTf)_2$ or CuOTf as copper source. Before presenting the results of the catalytic 1,4-additions, using phosphoramidites as ligands for copper, a brief review of dialkylzinc compounds will be given to show why these organometallic reagents are the nucleophilic carbon donors of choice for this reaction.

4.2 Organozinc compounds[1,2,3,4]

4.2.1 Historical perspective

The synthesis of dimethylzinc and diethylzinc from zinc and the corresponding alkyl iodide was described first by Frankland in 1849.[5] This was the first preparation of a compound with a metal-carbon σ-bond. After intensive research into the reactions of organozinc compounds it turned out that their poor reactivity towards electrophiles made these reagents not viable for synthetic applications. After the successful electrochemical preparation of magnesium metal at the end of the 19th century, Barbier[6] and his student Grignard[7] succeeded in synthesizing organomagnesium reagents,[8] which replaced the pyrophoric organozinc compounds in organic synthesis. Apart from the Reformatsky reaction[9], the comeback of organozinc reagents started in 1942 with the synthesis of functionalized organozinc reagents.[10] The anticipated drawbacks of these reagents were turned into an advantage with the possibility to obtain organometallics reagents bearing functional groups. Further developments like the use of highly active “Rieke zinc”,[11] salt-free halogen-metal exchange[12] and salt-free transmetallation[13] make these organometallics one of the most useful carbon nucleophile donors in organic synthesis, especially in asymmetric carbon-carbon bond formation reactions.[14] Organozinc compounds are not only used for the production of fine

chemicals but also in polymerization reactions like Ziegler-Natter type systems (catalytic amounts) and polymerization of aldehydes, cyclic esters and lactones (stoichiometric amounts).[4]

4.2.2 Properties of organozinc compounds

There are three main classes of organozinc compounds: organozinc halides (RZnX), diorganozincs (R_2Zn) and zincates ($M^+R_3Zn^-$; M = Li, MgX).[1,2,3] The focus of this paragraph is on diorganozinc reagents because of their special properties and their importance for enantioselective catalytic C-C bond formation reactions. Furthermore, only saturated diorganozinc reagents will be discussed because the unsaturated analogs are described in sections 7.5.1 and 7.5.3.

Dialkylzinc compounds are colourless pyrophoric liquids and can explode spontaneously on exposure to with water. Diorganozinc compounds with linear carbon chains can be distilled without problem but dicycloalkylzinc reagents suffer from decomposition at temperatures above 45-60°C with simultaneous formation of zinc metal. In solution with aprotic solvents these compounds are not aggregated but exist as monomeric species. Due to the electronic structure of the ground state an sp-hybridization is assumed with a bond angle of 180°. The linear structure has been proven for Me_2Zn by IR and Raman spectroscopy,[15] force field calculations,[16] quantum chemical calculations[16] and photoelectron spectroscopy (Figure 4.1, **A**).[17] The measurements indicate a dipole moment of $\mu = 0$ for dialkylzinc compounds, which was confirmed for their heptane solutions.[18]

Dialkylzincs are electron deficient compounds and undergo formation of defined adducts with electron donating molecules especially with ethers,[19] amines,[20] and phosphines[21] (Figure 4.1, **B** and **C**). Crystallographic data show that the zinc atom is tetra-coordinated in theses adducts. The carbon-zinc-carbon angle has values between 136° and 148° and the carbon-zinc bond length is around 2Å which is comparable with the bond length of pure Me_2Zn (1.95Å). Furthermore, diorganozinc compounds can form π-complexes with aromatic compounds like benzene with a distance of 2.5-3.5Å between the aromatic ring and the metal center (Et_2Zn).[22]

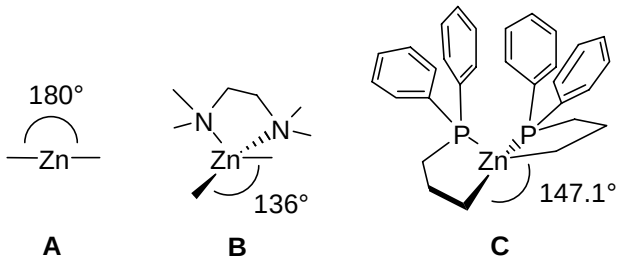


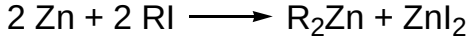
Figure 4.1 *C-Zn-C bond angles in different diorganozinc compounds.*

The distortion of the C-Zn-C bond angle in these adducts has a direct influence on the dipolar moment of the diorganozinc compounds. This dipole moment increases with the electronegativity of the organic moiety. With stronger polarity of the Zn-C bond the electron

acceptor strength increases. Typical dipolar moments for bis-amine complexes have values between μ = 1.7-2.7, whereas the π-complex of diethylzinc with benzene has a dipole moment of μ = 0.6.[18] This feature is important in understanding the reactivity of organozinc compounds.

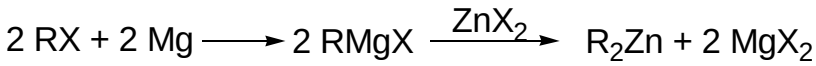
4.2.3 Synthesis of diorganozinc compounds

There are many syntheses of dialkylzinc compounds. The main procedures are presented in this section**.** The oldest method, and nowadays used for the industrial synthesis of diorganozinc compounds, is based on the reaction of alkyl iodides with zinc dust (
Scheme 4.1).



Scheme 4.1 *Synthesis of diorganozinc compounds with Zn and alkylhalides***.**

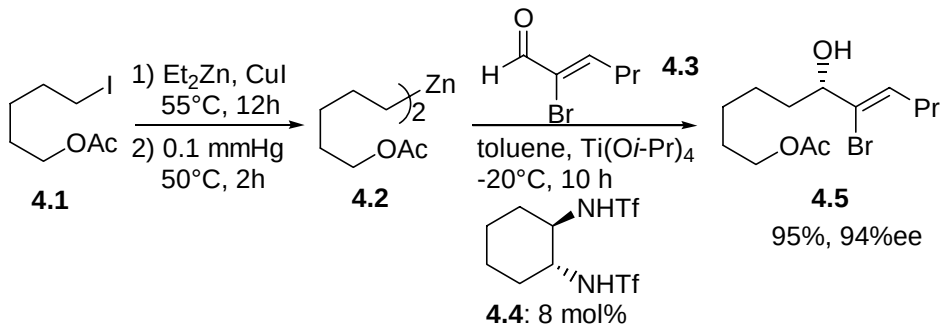
This synthesis is carried out under high pressure[23], or with a zinc alloy[24] under inert conditions and is only applicable for linear primary diorganozincs with a chain length of up to five carbon atoms. The reason for this limitation is the difficulty of purification of the diorganozinc compound from dimeric products and iodine.
One of the most general methods for the syntheses of diorganozinc compounds is the transmetallation reaction of organometallics reagents with zinc salts (Scheme 4.2).



Scheme 4.2 *Synthesis of diorganozinc compounds by transmetallation***.**

For this purpose organo-magnesium, -lithium, -sodium, -aluminum, -mercury and –thallium compounds can be used.[1] The most common method is based on the use of Grignard reagents (Scheme 4.2). The readily available halogen containing organic compounds are converted into the corresponding Grignard reagents in the presence of magnesium. Further treatment with anhydrous ZnX_2 in THF or diethyl ether gives the diorganozinc compounds, which can be purified by distillation. The drawback of this procedure is the intolerance of Grignard reagents towards functional groups. A number of different methods have been developed recently by the group of Knochel especially for the preparation of functionalized zinc reagents.[25]

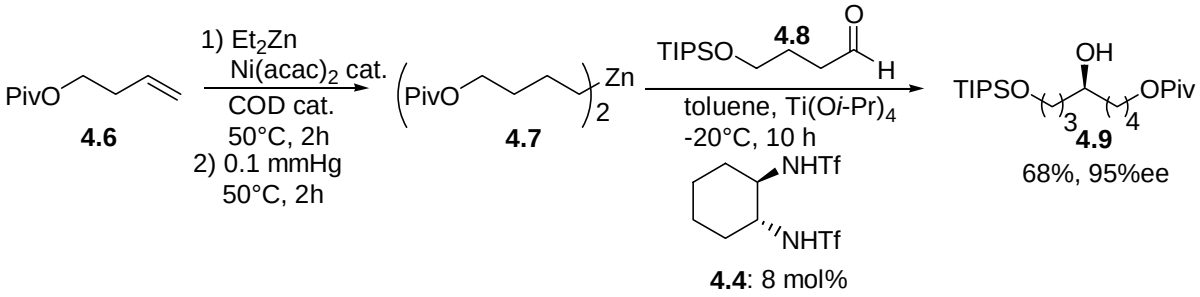
The first method involves the synthesis of diorganozinc compounds by an iodine (or bromine)–zinc exchange reaction.



Scheme 4.3 *Synthesis of diorganozinc compounds by an iodine–zinc exchange reaction.*

This reaction allows the conversion of primary alkyl iodides like **4.1** into functionalized diorganozinc **4.2** by treatment with diethylzinc. [26,27] This reaction, which proceeds via a radical intermediates, involves a solvent free system with a catalytic amount of Cu(I) salts at elevated temperatures. Low pressure was used to remove the excess of diethylzinc. The application of **4.2** was demonstrated by the asymmetric addition to aldehyde **4.3** in the presence of a Ti(O*i*-Pr)$_4$ / **4.4** catalyst to provide **4.5** in 95% yield and with 94% ee (Scheme 4.3).[26,27] Marcoux and Charette[28] used light as radical initiator without a copper catalyst to prepare functionalized diorganozinc reagents like **4.2**.

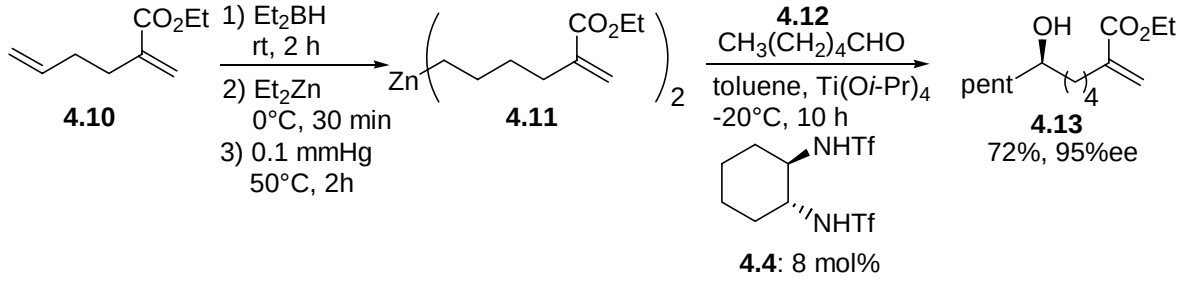
The nickel-catalyzed hydrozincation reaction represents another method to synthesize functionalized diorganozinc compounds (Scheme 4.4). [29,30]



Scheme 4.4 *Synthesis of organozinc compounds by a nickel catalyzed hydrozincation reaction.*

Direct hydrozincation of olefins is possible using diethylzinc in the presence of a catalytic amount of Ni(acac)$_2$ and COD (cyclooctadiene). The nickel salt is alkylated by diethylzinc and undergoes a β–hydrogen elimination to form a nickel hydride species and ethene. Exchange of the ethene ligand by the terminal alkene **4.6** and hydride addition gives a functionalized alkylnickel species. Alkyl ligand exchange with diethylzinc gives the functionalized zinc reagent and an ethyl nickel species which can undergo β–hydrogen elimination again. The driving force of this reaction is the release of ethene. The prepared organozinc compound **4.7** could be used in the asymmetric alkylation of aldehyde **4.8** in the presence of the Ti(O*i*-Pr)$_4$ / **4.4** catalyst giving compound **4.9** in 68% yield and 95% ee.

Finally a method for the synthesis of functionalized organozinc compounds, developed in 1961, has recently experienced a comeback.[31] Functionalized boranes undergo a transmetallation reaction with neat diorganozinc reagents (Scheme 4.5).

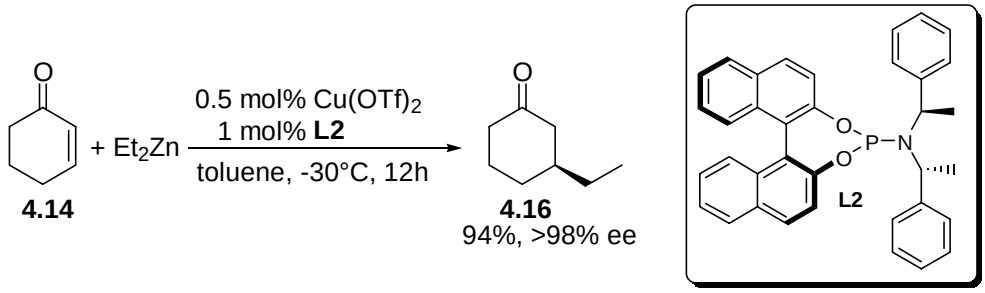


Scheme 4.5 *Synthesis of diorganozinc compounds by a boron-zinc exchange reaction*.[32,33,34]

Using this method salt-free and thermally unstable diorganozinc reagents can be synthesized. Terminal alkene **4.10** undergo a hydroboration reaction with diethylborane giving a functionalized borane. Transmetalation with diethylzinc proceeds at room temperature. Evaporation of the formed triethylboron, which is the driving force of this reaction, and the excess of diethylzinc gave compound **4.11**. The synthesized diorganozinc compound **4.11** undergoes a 1,2-addition with hexanal **4.12** in the presence of a Ti(O*i*-Pr)$_4$ / **4.4** catalyst affording **4.13** in 72% yield and with 95% ee (Scheme 4.5).

4.3 Catalytic asymmetric 1,4-addition of dialkylzincs to 2-cyclohexenone using phosphoramidite L2

In section 2.3 a review of the catalytic asymmetric 1,4-addition of dialkylzinc reagents to enones was given. During my undergraduate research new phosphoramidite ligands for copper were prepared and we were very pleased with the discovery of phosphoramidite **L2**. The first experiments confirmed that the replacement of the achiral amine part of **L19** by a chiral structural unit had an enormous influence on the enantioselectivity of the 1,4-addition.

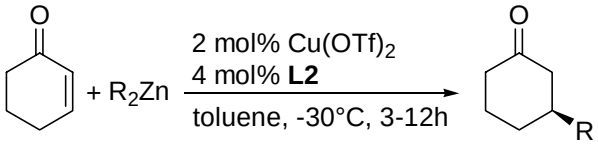


Scheme 4.6 *Enantioselective 1,4-addition catalyzed by Cu(OTf)$_2$/ **L2**.*

The reaction of 2-cyclohexenone **4.14** and diethylzinc in the presence of 0.5 mol% Cu(OTf)$_2$ and 1 mol% **L2** in toluene at –30°C gave after 12h the 1,4-addition product **4.16** in 94% yield and >98% ee (Scheme 4.6).[35] The absolute stereochemistry (S)-**4.16** was determined by X-ray analysis (see section 4.4). These results represented the first examples of absolute stereocontrol in the catalytic asymmetric 1,4-addition. This breakthrough provided the basis for the experiments discussed in this chapter.

These results also stimulated an investigation into the use of different dialkylzinc reagents for this reaction to see if the enantioselectivity is influenced by the organometallic reagent.[36] In these studies 2 mol% of $Cu(OTf)_2$ and 4 mol% of **L2** were used, because of the lower reactivity of organozincs with a longer alkyl chain. Furthermore, **4.14** was used as substrate and the reaction was carried out at –30°C in toluene and stopped after full conversion of the starting material (as determined by TLC). The results are summarized in Table 4.1.

Table 4.1 *Results of the catalytic asymmetric 1,4-addition of dialkylzinc reagents to* ***4.11****.*



4.14 **4.15 - 4.23**

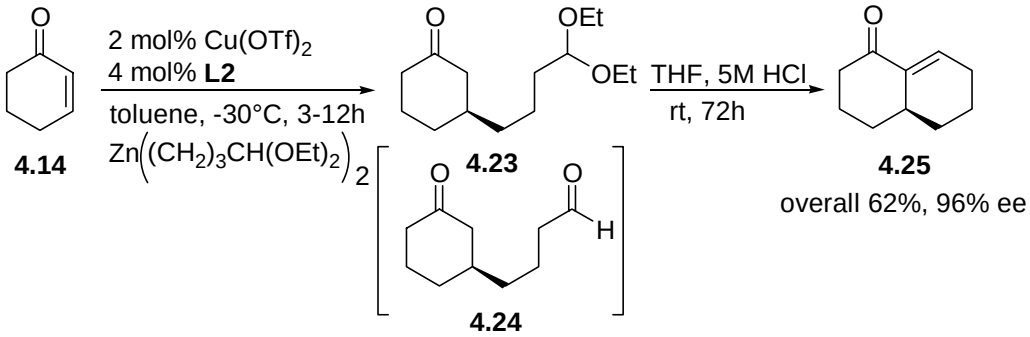
entry	R_2Zn[a]	adduct	yield (%)[b]	ee (%)[c]
1	CH_3	**4.15**	72	>98
2	CH_2CH_3	**4.16**	94	>98
3	CH_2CH_3[h]	**4.16**	68	0
4	$(CH_3)_2CH$[37]	**4.17**	95	73[d]
5	$(CH_3)_2CH$	**4.17**	92	82[e]
6	$(CH_3)_2CH$	**4.17**	95	94[f]
7	*n*-C_7H_{15}[38]	**4.18**	95	95
8	$(CH_2)_3Ph$[39]	**4.19**	53	95
9	$(CH_2)_6Br$[39]	**4.20**	25	95
10	$(CH_2)_5OAc$[39]	**4.21**	77	95
11	$(CH_2)_6OPiv$[39]	**4.22**	87	93
12	$(CH_2)_3CH(OEt)_2$[39]	**4.23**	91	97
13	$(CH_2)_3CO_2Et$[28]	-	-	-
14	$CH_2CH=CH_2$[40]	**4.26**	52[g]	n.t.

[a] NMR data are given in the experimental section; [b] isolated yield [c] determined by ^{13}C-NMR spectroscopy after derivatization with 1,2-diphenyl ethylenediamine,[41] [d] adding neat *i*-Pr_2Zn; [e] 1M solution in toluene, [f] reaction temperature –80°C; [g] 1,2-addition product; [h] EtZnCl[42]

Using dimethylzinc in this reaction the process was slower in comparison with diethylzinc (for a comparison of reaction rates of dialkylzincs in the copper catalyzed 1,4-addition see, ref. 58). The volatile product **4.15** was isolated in 72% yield with an ee value higher than >98% (Table 4.1, entry 1). The isolated yield of 3-ethylcyclohexanone was significantly higher because purification of the reaction mixture by column chromatography was performed without evaporation of the solvent (toluene). The separation of solvent (toluene) and product **4.16** by distillation caused a dramatic decrease of the yield. The ee of **4.16** was >98% (Table 4.1, entry 2). Using EtZnCl, freshly prepared from Et_2Zn and $ZnCl_2$,[42] **4.16** was obtained in moderate yield and with no enantiomeric excess at all (Table 4.1, entry

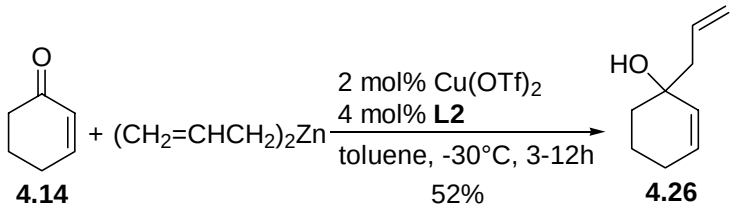
3). The reason might be the different chemical properties of alkylzinc halides compared to dialkylzinc species.[4] The use of diisopropylzinc as nucleophilic carbon source had a dramatic impact on the selectivity of the reaction. The reaction was faster in comparison with the 1,4-addition using diethylzinc. Adding diisopropylzinc neat to the reaction mixture gave **4.17** with an ee value of 72% (Table 4.1, entry 4). The selectivity increased to 82% ee by using a 1M solution of *i*-Pr_2Zn in toluene (Table 4.1, entry 5). Performing the reaction at –80°C complete conversion after 18 h was achieved and the ee for **4.17** could be increased to 94% (Table 4.1, entry 6). The isolated yield of **4.17** was excellent in all cases. The less reactive reagent diheptylzinc gave product **4.18** in 95 % yield with 95% ee (Table 4.1, entry 7). Furthermore, the functionalized diorganozinc reagents, synthesized by the method of Knochel, provided in all cases high enantioselectivities in the 1,4-addition. The yield of **4.19** using di-(3-phenylpropyl)zinc was 53% and the enantioselectivity was 95% (Table 4.1, entry 8). A low yield (25%) was obtained for **4.20** using di-(6-bromohexyl)zinc. Perhaps a competing reaction of the organozinc moiety with the resulting zinc enolate (bromide substitution) occur. The ee value (95%) for **4.20** was excellent (Table 4.1, entry 9). The organozinc reagents with a protected alcohol functionality, di-[5-(acetyloxy)pentyl]zinc and di-{6-[(2,2-dimethylpropanoyl)oxy]hexyl}zinc gave the 1,4-addition products **4.21** and **4.22** in good yields (77% and 87%) and with excellent enantioselectivities of 95% and 93%, respectively (Table 4.1, entries 10, 11). The novel zinc reagent di-(4,4-diethoxybutyl)zinc was successfully applied achieving of 97%ee for product **4.23** (Table 4.1, entry 12). Work-up with 1M HCl (aq) gave a mixture of compounds **4.23** and **4.24**. Using a NH_4Cl (aq) solution as quenching reagent, however, **4.23** was obtained exclusively in 91% yield.

Treating **4.23** with an acidic THF solution an intramolecular aldol reaction was observed yielding to the corresponding bicyclic system **4.25** (Scheme 4.7). This compound was obtained in an overall yield of 62% and with an ee of 96%. Further investigations along these lines have been carried out by Robert Naasz.[43]



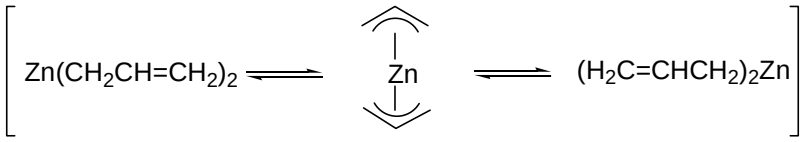
Scheme 4.7 *Cyclization of compound **4.23** to a bicyclic ring system.*

Using functionalized zinc reagent (di(3-ethoxy-3-oxopropyl)zinc), synthesized by the procedure of Marcoux and Charette,[28] no 1,4-addition product was obtained under the reaction condition of the catalytic asymmetric 1,4-addition (Table 4.1, entry 13). Furthermore, the catalytic 1,4-addition of diallylzinc to 2-cyclohexenone gave only the 1,2-addition product **4.26** in 52% yield (Table 4.1, entry 13 and Scheme 4.8).



Scheme 4.8 *Addition of diallylzinc to 2-cyclohexenone.*

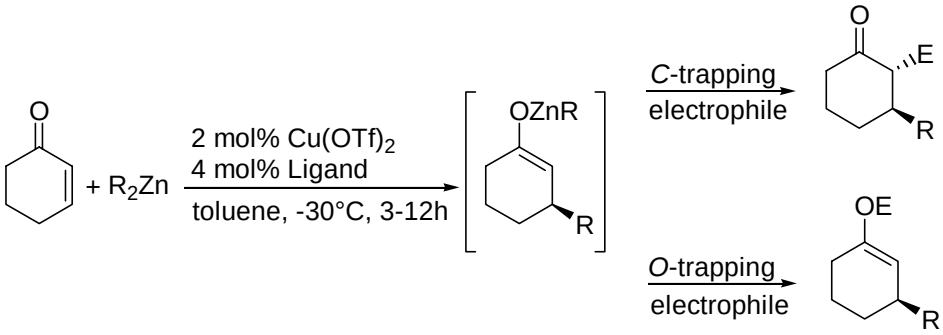
A reason for this behavior might be the special bond properties of diallylzinc.[40] The differences with other dialkylzinc reagents are that diallylzinc is a yellow solid, sensitive to light, insoluble in hydrocarbons and only moderately soluble in benzene and toluene. The ^{1}H-NMR-spectrum shows a dynamic allylic system,[44] which might be explained by a fast equilibrium as depicted in Scheme 4.9.[1]



Scheme 4.9 *Equilibrium of diallylzinc.*

4.4 Catalytic asymmetric 1,4-additon-enolate trapping reactions

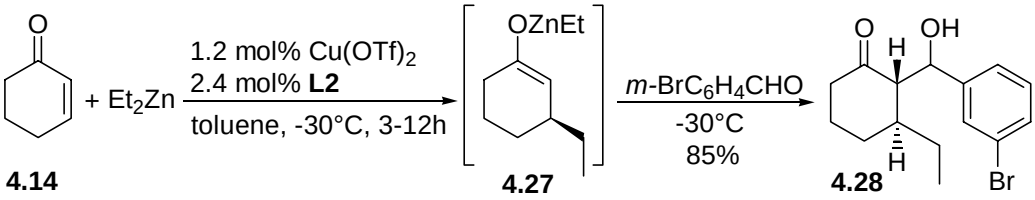
The 1,4-addition–enolate trapping reaction is a tandem reaction which has been used intensively in organic synthesis.[45,46,47] Most of these enolate trapping protocols involve the use of cuprates for the 1,4-addition resulting in the formation of lithium enolates. The use of zinc enolates in enolate-trapping reactions has been less investigated. In this reaction the *in situ* formed zinc enolate is not protonated to obtain the corresponding 3-substituted ketone but rather treated with an electrophiles. Scheme 4.10 illustrates the scope of this process and emphasizes the fact that enolates can undergo *O*-and/or *C*-trapping, the site of attack depending mainly on the choice of eletrophilic trapping reagents. C-Enolate trapping results in the regiospecific synthesis of α,β-disubstituted ketones and with a high degree of stereoselectivity especially in case of cyclic ketones. O-Enolate trapping, in contrast, results in the regioselective formation of a stable enol ether which can be used as chiral nucleophile is other reaction. In most cases this reaction is applied if the zinc enolate cannot be used as an *in situ* generated compound.



Scheme 4.10 *Catalytic asymmetric 1,4-addition-enolate trapping reactions.*

4.4.1 Catalytic asymmetric 1,4-additon-enolate trapping reactions reported in literature

The first trapping reaction of enantiomerically pure zinc enolates was carried out with aldehydes as electrophiles. Based on the findings of Noyori,[48] different aldehydes were investigated as electrophiles in the so-called catalytic enantioselective tandem 1,4-addition-aldol reaction explored in our group (Scheme 4.11). [35,43,49]



Scheme 4.11 *Catalytic enantioselective tandem 1,4-addition-aldol reaction.*

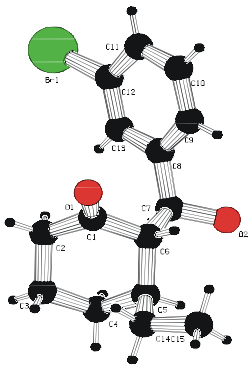


Figure 4.2 X-ray structure of **4.28**.

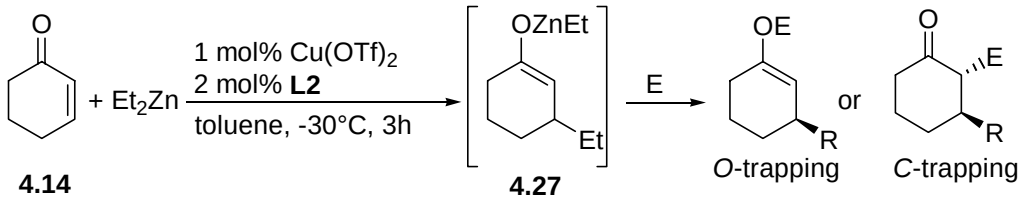
A typical example was the reaction of **4.14** and diethylzinc in the presence of 1.2 mol% $Cu(OTf)_2$/**L2** affording after addition of *m*-BrC_6H_4CHO to the formed zinc enolate **4.27**,the tandem adduct **4.28** in 85% yield (Scheme 4.11). Unfortunately almost no selectivity was detected in the subsequent aldol step giving a *threo:erythro* ratio of 1:1. X-ray analysis proved the *all-trans* selectivity of **4.28** as well as the absolute stereochemistry (6S, 7S, 7S) of **4.28** (Figure 4.2).

Enantiomerically pure zinc enolates, obtained from 1,4-additions using the $Cu(OTf)_2$/**L2** catalyst, were also trapped in a palladium catalyzed allylation reaction with allylic acetate.[43] The corresponding products were obtained in high yield and with a *trans:cis* ratios of 9:1. Alexakis reported that theses zinc enolates could also be trapped with acetals in the presence of $BF_3 \bullet Et_2O$ affording the corresponding 3-alkoxy ketone in good yield with a 100% *trans* selectivity but with 50:50 ratio of *erythro:threo* configuration.[50] Applying chiral acetals and TMSOTf as Lewis acid full stereocontrol was achieved in the subsequent trapping reaction. The alkylation of an enantiomerically pure zinc enolate was realized by Hoveyda,[51] using a primary alkyl iodide in the presence of 10 eq. of HMPA (Table 4.2, entry 4). The α-alkylation product was obtained in 80% yield and with a *trans:cis* selectivity of 15:1. Recently the same group reported about an intramolecular α-alkylation with primary tosylates to proceed *in situ* without additives.[52]

4.4.2 New asymmetric catalytic 1,4-addition-enolate trapping reactions

Enolate trapping procedures that have been successful applied using cuprates for the 1,4-addition[46] were used to convert enantiomerically pure zinc enolates. The reaction was carried out with 2-cyclohexenone and diethylzinc in the presence of a $Cu(OTf)_2$/**L2** catalyst affording the zinc enolate which was treated with different electrophiles. The results are summarized in Table 4.2.

Table 4.2 *Catalytic enantioselective 1,4-addition-enolate-trapping reactions.*



4.14 **4.27**

entry	C-/O-trapping	trapping reagent	product	yield (%)
1	O-trapping	$ClP(O)(OEt)_2$	vinylphosphate	76
2	O-trapping	Ac_2O	acetoxy enolate	n.d.[a]
3	O-trapping	TMSCl	trimethylsiloxy enolate	n.d.[a]
4	C-trapping	allyl bromide, rt, 3d	allylation product	13
5	C-trapping	ethylene oxide	no conversion	-
6	C-trapping	$ClP(OEt)_2$	complex reaction mixture	-
7	C-trapping	CH_3COCl	no conversion	-

[a] ^{1}H-NMR experiment.

The first trapping reaction was carried out with $ClP(O)(OEt)_2$ as electrophile giving a vinylphosphate in 76% yield (Table 4.2, entry 1). This product is stable and was purified by column chromatography. Other *O*-trapping reactions were carried out on and the products were analyzed by ^{1}H-NMR. The use of TMSCl and acetic anhydride gave the corresponding enol ether vs. enol ester at ambient temperature (Table 4.2, entries 2 and 3).[53] Furthermore,

C-trapping reactions were carried out as originally described for lithium enolates.[46] Treating the chiral zinc enolate **7.24** with allylic bromide at room temperature for 3 d gave 13% of the allylation product with incomplete conversion (Table 4.2, entry 4). Although ethylene oxide undergoes a nucleophilic epoxide opening reaction with lithium enolates[54] no reaction was observed using **4.27** and ethylene oxide (Table 4.2, entry 5). The use of $ClP(OEt)_2$ to obtain the corresponding α-phosphono esters[55] in the presence of air was unsuccessful as was the use of acetyl chloride to prepare the corresponding diketones (Table 4.2, entries 10 and 11).[56]

4.4.3 The nature of zinc enolates

The experiments summarized in section 4.4.2 prove a different behavior of lithium and zinc enolates. In general lithium enolates are more reactive than the corresponding zinc enolates. But what is the reason?

Reformatsky reagents have been investigated by Boersma and have been shown to be dimeric, both in solution (molecular weight measurements) and in the solid state (X-ray crystal structure) (Figure 4.3, **A**).[57] Furthermore, these species exist neither as a C-metallated species nor as an enolate, but rather as a combination of the two. Ketone zinc enolates, in contrast, are believed to exist only in the enol-form and not in the keto-form as was established by ^{1}H-NMR and ^{13}C-NMR spectroscopy (Figure 4.3, **B**).[58] Molecular weight measurement by a cyroscopic method revealed that the aggregation state of the zinc enolate in benzene is dimeric, too (Figure 4.3, **C**).[58]

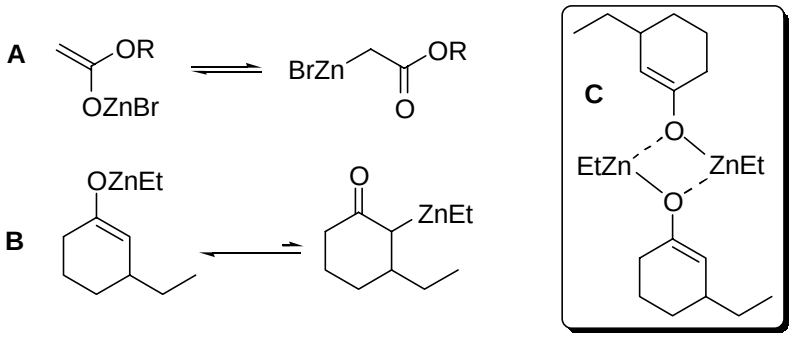


Figure 4.3 *Zinc enolate-equilibriums and aggregation states.*

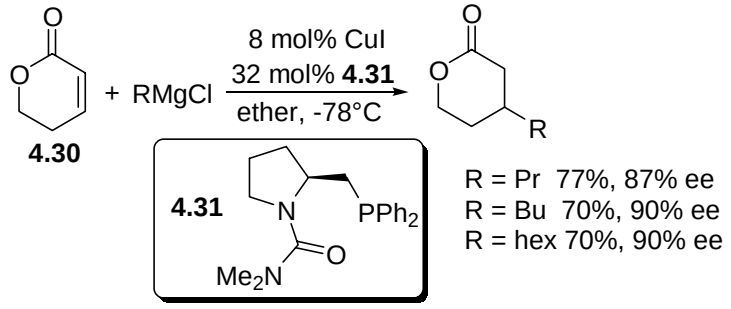
The aggregation of the zinc enolates and the resulting equilibriums might be the reasons for the reduced reactivity in comparison with lithium enolates.

4.5 Catalytic asymmetric 1,4-addition to unsaturated lactones

4.5.1 Introduction

The asymmetric 1,4-addition of diorganozinc reagents to α,β-unsaturated lactones has been developed as an extension of the asymmetric 1,4-addition to enones. Although

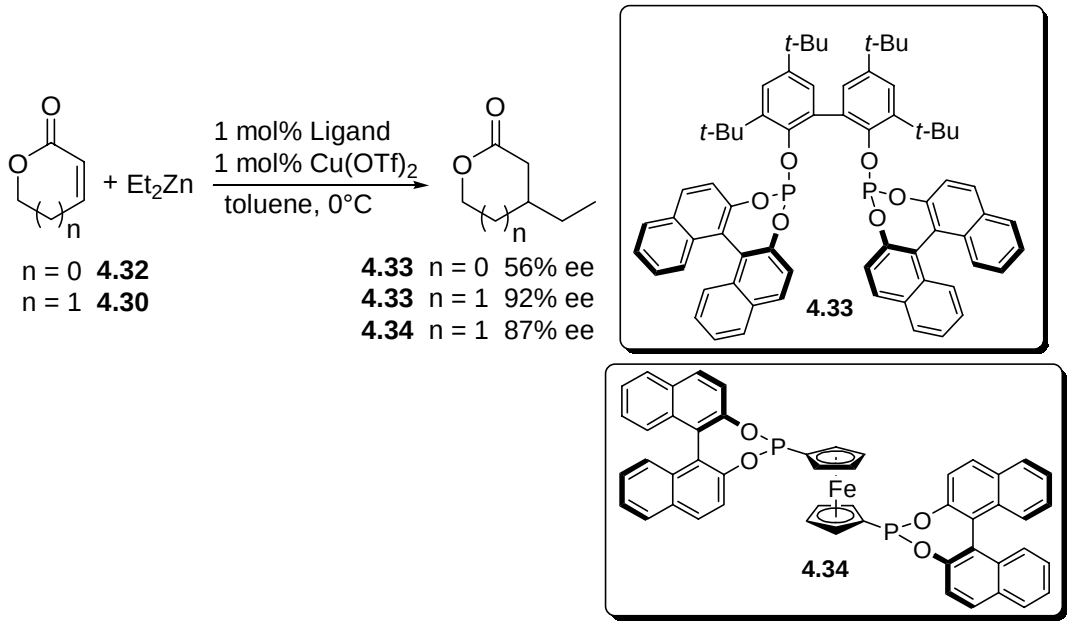
α,β–unsaturated α,α–diesters[59] and α,β–unsaturated α,α-nitroester[60] smoothly underwent a catalytic asymmetric 1,4-addition with ee's up to 92%, acyclic α,β-unsaturated monoesters were not reactive under these conditions. Therefore, it was surprising that unsaturated lactones gave a clean reaction at –30° in toluene with diethylzinc in the presence of a copper catalyst. The first asymmetric catalytic 1,4-addition to unsaturated lactones was reported by Tomioka.[61]



Scheme 4.12 *The first catalytic asymmetric 1,4-addition to an α,β–unsaturated lactone.*[61]

Using Grignard reagents in the presence of 8 mol% CuI and 32 mol% of ligand **4.31** lactone **4.30** underwent 1,4-additions at –78°C (Scheme 4.12). The corresponding products were isolated in high yield with enantioselectivities up to 90%.

Later Chan reported the first catalytic asymmetric 1,4-addition to unsaturated lactones in the presence of 1 mol% of a $Cu(OTf)_2$ / **4.33** catalyst employing diethylzinc instead of Grignard reagents.[62] Five-membered and six-membered unsaturated lactones could be converted with ee values of 56% and 92%, respectively (Scheme 4.13). Recently Reetz reported the catalyst $Cu(OTf)_2$ / **4.34**, achieving 87% ee in the asymmetric 1,4-addition of diethylzinc to **4.30**.[63]

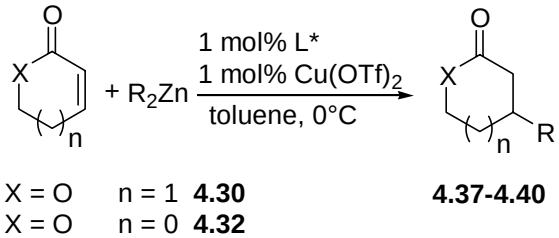


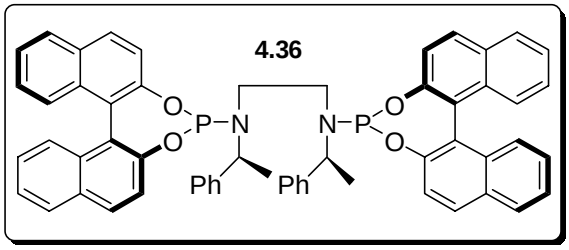
Scheme 4.13 C*atalytic asymmetric 1,4-addition of diethylzinc to α,β–unsaturated lactones.*

4.5.2 Cu(OTf)$_2$-phosphoramidite catalyzed 1,4-addition to unsaturated lactones

Because phosphoramidites are very successful ligands for the 1,4-addition of diorganozinc reagents to enones, unsaturated lactones were applied as substrates too. The reaction of different unsaturated lactones and diethylzinc was carried out in toluene at 0°C in the presence of Cu(OTf)$_2$ / phosphoramidite catalysts. The results are summarized in Table 4.3.

Table 4.3 *Catalytic asymmetric 1,4-addition of dialkylzinc to unsaturated lactones using Cu(OTf)$_2$/ phosphoramidite catalysts.*





entry	L*	lactone	R_2Zn	adduct	conv. %[a]	ee %[b]
1	**L19**	**4.30**	Et	**4.37**	70	17
2	**L2**	**4.30**	Et	**4.37**	100	42
3	**L2**	**4.30**	Et	**4.37**	88	24[c]
4	**L2**	**4.30**	Me	**4.38**	61	21[d]
5	**L2**	**4.30**	Bu	**4.39**	95	-[e]
6	**L6**	**4.30**	Et	**4.37**	75	14
7	**L5**	**4.30**	Et	**4.37**	54	49[f]
8	**4.36**	**4.30**	Et	**4.37**	4	46
9	**L2**	**4.32**	Et	**4.40**	45	-[e]
10	**L2**	**4.35**	Et	-	-	-

[a] after 3 h measured by GC; [b] determined by GC, A-TA column (not baseline separated); [c] reaction temperature –30°C; [d] baseline separated, [e] no separation on chiral GC; [f] other enantiomer.

The 1,4-addition of dialkylzincs to unsaturated lactones catalyzed by chiral copper / phosphoramidite complexes is successful, although it was previously indicated otherwise.[64] Using ligand **L19** in the 1,4-addition of diethylzinc to **4.30** gave **4.37** with 17% ee and 70% conversion after 3 h (Table 4.3, entry 1). Using ligand **L2** 100% conversion took place after 3 h at 0°C and the enantiomeric excess for **4.37** could be enhanced to 42% (Table 4.3, entry 2). Interestingly, lowering the reaction temperature to –30°C gave 88% conversion of **4.30** and a lower enantioselectivity of 24% using the same ligand **L2** (Table 4.3, entry 3). The use of different diorganozinc reagent namely Me_2Zn gave adduct **4.38** with 21% ee with a conversion of 61% after 3 h at 0°C (Table 4.3, entry 4). In the catalytic 1,4-addition of **4.30** with dibutylzinc almost full conversion was reached after 3 h but unfortunately no separation of the enantiomers of **4.39** was achieved by chiral GC analysis (Table 4.3, entry 5). Using ligand **L6** 75% conversion after 3 h was achieved with 14% ee for **4.37** (Table 4.3, entry 6). It should be noted that the use of the other diastereomeric ligand of **L6**, **L5** changed the absolute stereochemistry of the product. A match-mismatch behavior could also be

recognized resulting in a higher ee value of 49% for **4.37** with 54% conversion after 3 h (Table 4.3, entry 7). Using the bidentate ligand **4.36** resulted in a very low conversion of 4% after 3 h and an enantiomeric excess of 46% (Table 4.3, entry 8). 2(5*H*)-furanone **4.32** was also used as a substrate. Applying ligand **L2** resulted in 45% conversion after 3 h at 0° but unfortunately no separation of the enantiomers of **4.40** could be achieved by chiral GC analysis (Table 4.3, entry 9). Furthermore it has been proven that unsaturated lactam **4.35** was not suitable as a substrate for the catalytic asymmetric 1,4-additon with diorganozinc compounds (Table 4.3, entry 10).
The remarkable feature that cyclic lactones in contrast to acyclic ester are suitable as substrates in the catalytic asymmetric 1,4-addition might be caused by the ring situation or the *s-cis* conformation of the C=C-C=O motif. So far now moderate ees have been achieved with phosphoramidite ligands in this reaction but ligand screening might deliver a selective phosphoramidite ligand also for this reaction.

4.6 Summary and concluding remarks

In this chapter first a brief review of dialkylzinc reagents is given. These linear organometallics have a dipole moment of $\mu = 0$. This could be a reason for their poor reactivity towards electrophiles. They form defined adducts with electron donating compounds (Lewis bases) which has a direct influence on their dipole moment of the C-Zn bond. The increasing polarity of the C-Zn bond has a strong influence on their reactivity towards electrophiles. The synthesis of these compounds has been discussed as well as their unique feature as organometallic reagents being tolerant to functional groups. They are used extensively in the catalytic asymmetric 1,4-addition as the nucleophilic source. In this chapter the catalytic asymmetric 1,4-addition of dialkylzinc reagents to 2-cyclohexenones catalyzed by a unique $Cu(OTf)_2$ / phosphoramidite **L2** catalyst is presented. For a variety of dialkylzinc reagents the corresponding β-substituted ketones could be obtained in high yield and with very high enantiomeric excesses. Absolute stereocontrol was obtained using dimethylzinc and diethylzinc. A different reaction mode was encountered using diallylzinc giving the 1,2-addition product only. An application of this reaction is presented in the synthesis of nearly optically pure [6,6]-carbobicyclic ring system, a method which is equivalent to the Hajos-Parrish ring annulation. Instead of protonation of the formed zinc enolate to obtain the corresponding β-substituted ketones, electrophiles can be used for α–functionalization or for the synthesis of stable enantiomerically pure enolates. Literature examples as well as new experiments are presented. Furthermore, a short discussion is given on the nature of zinc enolates. Discussed is finally the catalytic asymmetric 1,4-addition of dialkylzinc reagents to unsaturated lactones which proceeded with moderate enantioselectivities using phosphoramidite ligands.

Acknowledgement: Prof. Dr. Mauro Pineschi is gratefully acknowledged for his contributions to the catalytic asymmetric 1,4-addition and tandem 1,4-addition-aldol reaction. He performed the tandem 1,4-addition-aldol reactions and determined the absolute stereochemistry of the 1,4-addition products by recording an X-ray structure (Figure 4.2). Thanks also to Alessandro Mandoli for his work on the enolate-trapping reactions and the synthesis of compound **4.27** and **4.36**. Furthermore I would like to thank Robert Naasz for his collaboration in general but also for his advanced work on the catalytic enantioselective annulations.

4.7 Experimental section

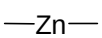
4.7.1 Material

For general information, see chapter 3. The preparation of dialkylzinc reagents was carried out with exceptional care because neat Et_2Zn is highly **pyrophoric** and can **explode** in contact with water.[1] The evaporated Et_2Zn in the cooled trap should be quenched with acetone in the trap, immediately after removal from the liquid N_2. Me_2Zn, Et_2Zn and Bu_2Zn are commercially available. EtZnCl, *i*-Pr_2Zn, Hep_2Zn and diallylzinc were synthesized using the given references. The distillation of *i*-Pr_2Zn, Hep_2Zn should be done with extreme care. For the destruction of pure diorganozinc compounds they should be diluted first with petrol ether and destroyed by adding acetone carefully. Take into account that *i*-Pr_2Zn is the most reactive organozinc compound, which can **explode** in contact with air. The functionalized zinc reagents were prepared by the *Knochel* method.[25,32] The unsaturated ketones and lactones are commercially available and were used without further purification.

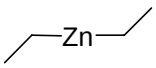
General procedure for synthesis of functionalized diorganozinc reagents:[25,32]
(Argon atmosphere): $HBEt_2$ (21 mmol, 1.2 M) was freshly prepared by adding 14 ml BEt_3 (1 M in THF) slowly to a cooled (-20°C) solution of 3.5 ml $BH_3 \cdot H_2S$ (2 M in diethyl ether) without stirring. After 10 min at –20°C the solution was warmed to 0°C and stirred slowly for an additional 10 min. The alkene (20 mmol) was cooled with liquid nitrogen and degassed under vacuum. The solution of $HBEt_2$ was added slowly to alkene at -20°C without stirring. After 1 h at 0°C without stirring the cooling bath was removed and the reaction mixture was stirred at room temperature. The conversion was controlled by ^{1}H-NMR or by oxidation of an aliquot of the solution with H_2O_2/ NaOH and analysis with GC. After complete conversion the volatiles were removed at **0°C** under vacuum (0.05 mmHg). The pure organoborane was treated with pure diethylzinc (2.2 ml, 18 mmol) at 0°C affording a dark colored mixture after some minutes. After stirring for 0.5 h at 0°C and 0.5 h at ambient temperature the excess of Et_2Zn and formed BEt_3 were pumped off (0.05 mmHg, 0°C, 2 h). The compound was diluted with toluene and the solvent (and traces of Et_2Zn) evaporated again, this time at room temperature. This procedure can be repeated and afterwards evaporation at room temperature is carried out for 12 h until no Et_2Zn was present (NMR).

All diorganozinc reagents were stored as a 1.0 M solution in toluene at -15°C. On large scale synthesis the diorganozinc should be diluted with toluene and filtrated because the formation of metallic zinc catalyze the decomposition of the diorganozinc reagent.

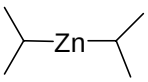
NMR-data of diorganozinc reagents ($CDCl_3$):



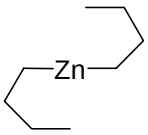
Dimethylzinc:
^{1}H-NMR (200 MHz) δ = -0.52 (s, 6H); ^{13}C-NMR (200 MHz) δ = -6.5.



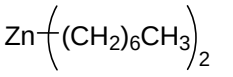
Diethylzinc:
^{1}H-NMR (200 MHz) δ = 1.14 (t, *J* = 8.5 Hz, 6H), 0.28 (q, *J* = 9 Hz, 4H); ^{13}C-NMR (200 MHz) δ = 10,1, 6.5.



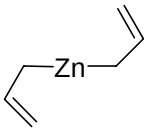
Di-*i*-propylzinc:[37]
^{1}H-NMR (200 MHz) δ = 1.17 (m, 2H), 0.70 (t, *J* = 5.1 Hz, 12H); ^{13}C-NMR (200 MHz) δ = 21.4, 18.4.



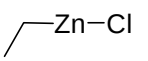
Di-*n*-butylzinc:
^{1}H-NMR (200 MHz) δ = 1.54 (m, *J* = 7.6 Hz, 4H), 1.29 0.28 (m, *J* = 7.6 Hz, 4H), 0.90 (t, *J* = 7.5 Hz, 6H), 0.37 (t, *J* = 7.6 Hz, 4H); ^{13}C-NMR (200 MHz) δ = 29.4, 28.7, 15.9, 14.1.



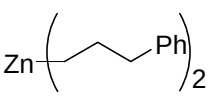
Di-*n*-heptylzinc:[38]
^{1}H-NMR (200 MHz) δ = 1.54 (m, 4H), 1.27 (m, 16H), 0.88 (t, *J* = 7.6 Hz, 6H), 0.36 (t, *J* = 7.6 Hz, 4H); ^{13}C-NMR (200 MHz) δ = 36.6, 32.0, 29.3, 26.4, 22.8, 16.1, 14.0.



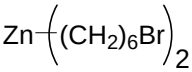
Diallylzinc:[40]
solid, yellow crystals, used as suspension in toluene: ^{1}H-NMR (200 MHz) δ = 6.03 (m, 2H), 2.95 (m, 8H) (dynamic allyl system); ^{13}C-NMR (200 MHz) broad signals δ = 140.4, 65.00, 29.8.



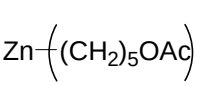
Ethylzinc chloride:[42]
^{1}H-NMR (200 MHz) δ = 1.19 (t, *J* = 8.0 Hz, 3H). 0.65 (m, *J* = 8.0 Hz, 2H); ^{13}C-NMR (200 MHz) δ = 11.0, 5.0.



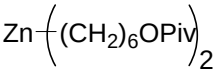
Di-(3-phenylpropyl)zinc:
^{1}H-NMR (200 MHz) δ = 7.23-7.01 (m, 10H), 2.39 (t, *J* = 7.6 Hz, 4H), 1.69 (m, 4H), -0.35 (t, *J* = 7.7 Hz, 4H);. ^{13}C NMR (200 MHz) δ = 143.0, 128.9, 128.7, 126.0, 40.1, 28.4, 12.5.



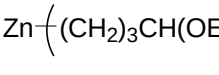
Di-(6-bromohexyl)zinc:
^{1}H-NMR (200 MHz) δ = 3.40 (t, *J* = 7.6 Hz, 4H), 1.83 (m, 4H), 1.53 (m, 4H), 1.41 (m, 4H), 1.16 (m, 4H), 0.34 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR (200 MHz) δ = 35.5, 34.1, 32.8, 28.0, 26.1, 16.0.



Di-[5-(acetyloxy)pentyl]zinc:
^{1}H-NMR (200 MHz) δ = 4.02 (t, *J* = 7.6 Hz, 4H), 2.02 (s, 6H), 1.54 (m, 8H), 1.32 (m, 4H), 0.34 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR (200 MHz) δ = 171.3, 64.7, 32.5, 28.4, 26.0, 21.0, 15.8.



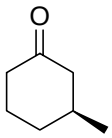
Di-{6-[(2,2-dimethylpropanoyl)oxy]hexyl}zinc:
^{1}H-NMR (200 MHz) δ = 4.00 (t, *J* = 7.6 Hz, 4H), 1.54 (m, 8H), 1.29 (m, 8H), 1.15 (s, 18H), 0.32 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR (200 MHz) δ = 178.6, 64.5, 38.7, 36.0, 28.6, 27.2, 26.2, 25.7, 13.8.



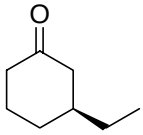
Di-(4,4-diethoxybutyl)zinc:
^{1}H-NMR (200 MHz) δ = 4.53 (t, *J* = 7.8 Hz, 2H), 3.67-3.45 (m, 8H), 1.61-1.58 (m, 8H), 1.16 (t, *J* = 7.6 Hz, 6H), 0.17 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR (200 MHz) δ = 103.8, 61.5, 60.6, 37.8, 21.5, 15.2, 13.2.

General procedure for the conjugate addition of diorganozincs to 2-cyclohexenone in the presence of Cu(OTf)$_2$ /L2 catalyst for compounds 4.15-4.27.

A solution of Cu(OTf)$_2$ (7.2 mg, 0.02 mmol) and phosphoramidite **L2** (21.5 mg, 0.04 mmol) in freshly distilled toluene (10 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. 2-Cyclohexenone (97 µl, 1 mmol) was added and the mixture was cooled to -30 °C. After adding a dialkylzinc reagent in toluene (1.1 M, 1 ml) the stirring was continued (–30°C). After complete conversion, the reaction mixture was poured into 25 ml 1M HCl (aq), the organic layer was separated, and the aqueous layer was twice extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.



(-)-(3S)-3-Methylcyclohexanone (4.15).
Purification by column chromatography (SiO_2 ether: hexane, 1:4) gave 80 mg (72%) of **4.15** as a colorless oil. ^{1}H-NMR (300 MHz) δ= 2.39-1.36 (m, 9H), 0.98 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (300 MHz) δ= 212.0, 49.9, 41.1, 34.1, 33.2, 25.2, 22.0; MS (EI) for $C_7H_{12}O$: m / z 112 (M^+), Determination of the ee of **4.15** was performed on a Astec G-TA, 30m x 0.25mm, He-flow 1.0 ml / min, isocratic 90°C, T_r = 14.1 min (S), T_r = 14.7 min (R).

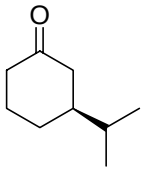


(-)-(3S)-3-Ethylcyclohexanone (4.16).
Purification by column chromatography (SiO_2 ether: hexane, 1:4) gave 78 mg (62%) of **4.16** as a colorless oil. ^{1}H-NMR (300 MHz) δ= 2.46-1.48 (m, 8H), 1.42-1.17 (m, 3H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (300 MHz) δ= 212.2, 47.8, 41.5,

40.8, 30.9, 29.3, 25.3, 11.1; MS (EI) for $C_8H_{14}O$: m / z 126 (M^+). Determination of the ee of **4.16** was performed on a Astec G-TA, 30m x 0.25mm, He-flow 1.0 ml / min, isocratic 95°C, T_r = 25.8 min (S), T_r = 27.2 min (R).

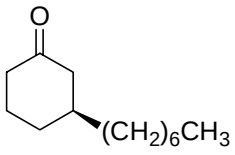
Determination of % ee by derivatization with 1,2 diphenylethylene diamine

The 1,4-addition adduct (0.2 mmol) was treated with 0.22 mmol of (R,R)-1,2-diphenyl ethylene diamine in $CDCl_3$ (2 ml) and stirred in the presence of molecular sieves (4Å) for 12 h at room temperature. The mixture was analyzed by ^{13}C NMR. The ee values were determined by integration of diastereomeric carbon atoms.



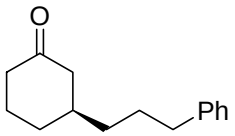
(3*S*)-3-Isopropylcyclohexanone (4.17).

Purification by column chromatography (SiO_2 ether: hexane, 1:6) gave 133 mg (95%) of **4.17** as a colorless oil. ^1H-NMR (200 MHz) δ = 1.95-2.41 (m, 5H). 0.86 (d, *J* = 5.1 Hz, 6H) 1.22-1.69 (m, 4H), 1.76-1.90 (m, 1H); ^{13}C NMR (200 MHz) δ = 212.7, 45.3, 45.2, 41.4, 32.3, 28.2, 25.4, 19.4, 19.1; HRMS calcd for $C_9H_{16}O$ 140.120, found 140.122. The ee of 94 % was determined by the ^{13}C NMR method.



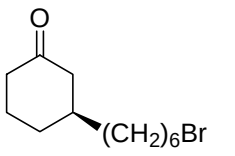
(3*S*)-3-Heptylcyclohexanone (4.18).

Purification by column chromatography (SiO_2 ether: hexane, 1:5, Rf = 0.67) gave 115 mg (92%) of **4.18** as a colorless oil. ^1H-NMR (200 MHz) δ = 1.46-2.44 (m, 8H). 1.24 (m, 13H), 0.86 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (200 MHz) δ = 212.3, 48.2, 41.4, 39.0, 36.5, 31.7, 31.2, 29.5, 29.1, 26.5, 25.2, 22.5, 14.0; HRMS calcd for $C_{13}H_{24}O$ 196.183, found 196.183. The ee of 95 % was determined by the ^{13}C NMR method.



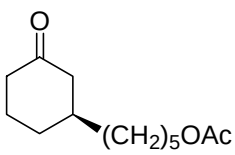
(3*S*)-3-(3-Phenylpropyl)cyclohexanone (4.19).

Purification by column chromatography (SiO_2 ether: hexane, 1:2, Rf = 0.67) gave 115 mg (53%) of **4.19** as a colorless oil. ^1H-NMR (200 MHz) δ = 7.22-7.37 (m, 5H), 2.66 (t, *J* = 7.8 Hz, 2H), 2.29-2.51 (m, 3H), 1.70-2.12 (m, 7H), 1.36-1.68 (m, 3H); ^{13}C NMR (200 MHz) δ = 211.9, 142.1, 128.3, 128.2, 125.7, 48.0, 41.4, 38.9, 36.0, 35.8, 31.1, 28.4, 25.2; HRMS calcd for $C_{15}H_{20}O$ 216.151, found 216.152. The ee of 95 % was determined by the ^{13}C NMR method.



(3*S*)-3-(6-Bromohexyl)cyclohexanone (4.20).

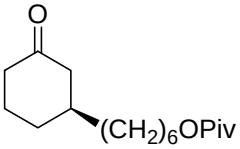
Purification by column chromatography (SiO_2 ether: hexane, 2:3, Rf = 0.64) gave 65 mg (25%) of **4.20** as a colorless oil. ^1H-NMR (200 MHz) δ = 3.36 (t, *J* = 7.6 Hz, 2H), 1.71-2.35 (m, 11H), 1.26-1.41 (m, 8H); ^{13}C NMR (200 MHz) δ = 212.2, 48.1, 41.4, 38.9, 36.3, 33.9, 32.6, 31.2, 28.7, 27.9, 26.4, 25.1; HRMS calcd for $C_{12}H_{21}OBr$ 261.085, found 261.084. The ee of 95 % was determined by the ^{13}C NMR method.



5-[(1*S*)-3-Oxocyclohexyl]pentyl acetate (4.21).

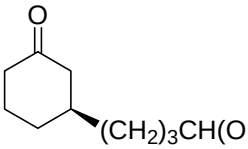
Purification by column chromatography (SiO_2 ether: hexane, 1:5, Rf = 0.26) gave 174 mg (77%) of **4.21** as a colorless oil. ^1H-NMR (200 MHz) δ

= 4.03 (t, *J* = 7.7 Hz, 2H), 2.22-2.47 (m, 2H), 2.03 (s, 3H), 1.55-2.00 (m, 8H), 1.31 (m, 7H); ^{13}C NMR (200 MHz) δ = 211.8, 171.0, 64.3, 48.0, 41.4, 38.8, 36.3, 31.2, 28.4, 26.2, 25.9, 25.1, 20.9; HRMS calcd for $C_{13}H_{22}O_3$ 226.157, found 226.158. The ee of 95 % was determined by the ^{13}C NMR method.



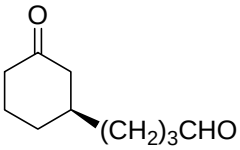
6-[(1*S*)-3-Oxocyclohexyl]hexyl pivaloate (4.22).

Purification by column chromatography (SiO_2 ether: hexane, 1:4, Rf = 0.28) gave 245 mg (87%) of **4.22** as a colorless oil. ^{1}H-NMR (200 MHz) δ = 4.00 (t, *J* = 7.8 Hz, 2H), 2.20-2.41 (m, 3H), 1.56-2.00 (m, 7H), 1.28 (m, 9H), 1.16 (s, 9H); ^{13}C NMR (200 MHz) δ = 212.0, 178.6, 64.3, 48.2, 41.5, 39.0, 38.7, 36.4, 31.3, 29.2, 28.5, 27.2, 26.5, 25.8, 25.3; HRMS calcd for $C_{17}H_{30}O_3$ 282.219, found 282.217. The ee of 93 % was determined by the ^{13}C NMR method.



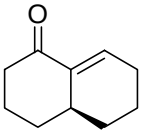
(3*S*)-3-(4,4-Diethoxybutyl)cyclohexanone (4.23).

Purification by column chromatography (SiO_2 ether: hexane, 2:3, Rf = 0.59) gave 220 mg (91%) of **4.23** as a colorless oil. ^{1}H-NMR (200 MHz) δ = 4.45 (t, *J* = 7.7 Hz, 1H), 3.44-3.64 (m, 4H), 2.31-2.38 (m, 3H), 1.54-2.02 (m, 6H), 1.32-1.37 (m, 6H), 1.18 (t, *J* = 7.8 Hz, 6H); ^{13}C NMR (200 MHz) δ = 211.7, 102.8, 61.1, 61.0, 48.1, 41.4, 39.0, 36.4, 33.7, 31.2, 25.2, 21.9, 15.3, 14.0; MS (EI) for $C_{14}H_{26}O_3$: m / z 242 (M^+). The ee of 97 % was determined by the ^{13}C NMR method.



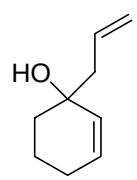
4-[(1*S*)-3-Oxocyclohexyl]butanal (4.24).

Purification by column chromatography (SiO_2 ether: hexane, 1:3, Rf = 0.50) gave **4.24** as colorless oil. ^{1}H-NMR (200 MHz) δ = 9.75 (s, 1H), 1.26-2.45 (m, 15H); ^{13}C NMR (200 MHz) δ = 211.4, 202.0, 47.9, 43.7, 41.3, 38.8, 35.8, 31.0, 25.1, 19.1; MS (EI) for $C_{10}H_{16}O_2$: m / z 168 (M^+).



(4a*S*)-3,4,4a,5,6,7-Hexahydro-1(2*H*)-naphthalenone (4.25).

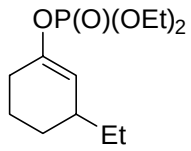
Compound **5e** (240 mg, 1 mmol) was dissolved in a solution of THF (22.5 ml), H_2O (5 ml) and conc. HCl (1.25 ml). After stirring for 72h at room temperature the reaction mixture was extracted three times with diethyl ether (10 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent the crude product (141 mg, 0.94 mmol) was obtained. Purification by column chromatography (SiO_2 ether: hexane, 1:3, Rf = 0.58) gave 93 mg (62%) of **4.25** as colorless oil. ^{1}H-NMR (200 MHz) δ = 6.69 (m, 1H), 1.10-2.61 (m, 13H); ^{13}C NMR (200 MHz) δ = 201.4, 140.0, 135.9, 40.2, 37.7, 31.5, 30.3, 26.1, 22.5, 21.3; HRMS calcd for $C_{10}H_{14}O$ 150.104, found 150.105. Determination of the ee of **4.25** was performed on a CP-cyclodex B, 30m x 0.25mm, He-flow 1.0 ml / min, isocratic 140°C, T_r = 24.25 min (S), T_r = 26.19 min (R).



1-Allyl-2-cyclohexen-1-ol (4.26).

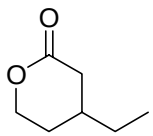
Purification by column chromatography (SiO_2 ether: hexane, 1:3, Rf = 0.32) gave 90 mg (65%) of **4.26** as a colorless oil. ^{1}H-NMR (200 MHz) δ = 5.94-5.78 (m, 2H), 5.63-5.56 (m, 1H), 5.15-5.05 (m, 2H), 2.11-1.85 (m, 2H), 1.28 (m, 2H), 1.74-1.54 (m,

4H). MS (EI) for $C_9H_{14}O$: m / z 138 (M^+).

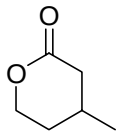


Diethyl 3-ethyl-1-cyclohexen-1-yl phosphate (4.27).
Instead of quenching NH_4Cl (aq), $ClP(O)(OEt)_2$ (0.25 ml, 1.7 mmol) was added and the reaction mixture was warmed to room temperature. After 3h at ambient temperature the reaction mixture was quenched with sat. NH_4Cl (aq), the organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 ethyl acetate: hexane, 1:4) gave 200 mg (76%) of **4.27** as a colorless oil. ^{1}H-NMR (200 MHz) δ = 5.41 (s, 1H), 4.15 (m, 4H), 2.18 (m, 2H), 2.11 (m, 1H), 1.83-1.57 (m, 3H), 1.41-1.13 (m, 3H), 1.37 (m, 6H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{31}P- NMR (200 MHz) δ = 6.6 Hz.

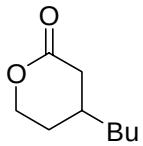
General procedure for the conjugate addition of dialkylzinc reagents to α,β-unsaturated lactones and a lactam employing a chiral catalyst derived from $Cu(OTf)_2$ and a phosphoramidite for compounds 4.37-4.40.
A solution of $Cu(OTf)_2$ (7.2 mg, 0.02 mmol) and a phosphoramidite (0.04 mmol) in freshly distilled toluene (10 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. The α,β-unsaturated lactone or lactam (1 mmol) was added and the mixture was cooled to -30 °C. After adding 1.0 ml of a dialkylzinc reagent in toluene (1.1 M) the stirring was continued (–30°C). After complete conversion, the reaction mixture was poured into 25 ml 1M HCl (aq), the organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.



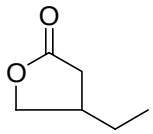
4-Ethyltetrahydro-2*H*-pyran-2-one (4.37).
Spectroscopic data in agreement with data in literature.[65]
Determination of the ee of **4.37** was performed on a Chiraldex A-TA, 30m x 0.25mm, He-flow 1.0 ml / min, oven temp.: 100°C, int. time: 3 min, rate : 10° / min, final temp.: 140°C, substrate 21.9 min., T_r = 22.4 min, T_r = 22.7 min.



4-Methyltetrahydro-2*H*-pyran-2-one (4.38).
Spectroscopic data in agreement with data in literature.[66]
Determination of the ee of **4.38** was performed on a Chiraldex A-TA, 30m x 0.25mm, He-flow 1.0 ml / min, oven temp.: 100°C, int. time: 3 min, rate: 5° / min, final temp.: 150°C, substrate 19.9 min., T_r = 16.6 min, T_r = 17.0 min.



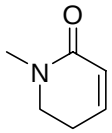
4-Butyltetrahydro-2*H*-pyran-2-one (4.39).
Spectroscopic data in agreement with data in literature.[67]
No separation of the enantiomers with chiral GC (A-TA, B-TA, G-TA and β-cyclodex and lipodex C).



4-Ethyldihydro-2(3*H*)-furanone (4.40).

Spectroscopic data in agreement with data in literature.[68]

No separation of the enantiomers with chiral GC (A-TA, B-TA, G-TA and β-cyclodex and lipodex C).



1-Methyl-5,6-dihydro-2(1*H*)-pyridinone (4.35).

A solution of lithium diisopropylamine, which was prepared from *n*-butyllithium (2.5M, 58 ml, 114 mmol) in hexane and diisopropylamine (20 ml, 144 mmol) in THF (50 ml), was cooled to –78°C. A solution of 1-methyl-2-piperidinone (4.5 ml, 40 mmol) in 50 ml THF was added dropwise and the reaction mixture was allowed to warm to –40°C during 1h. The mixture was again cooled to –78°C and treated with phenylselenenyl chloride (10 g, 52 mmol) in THF (30 ml). After 5 min the reaction was quenched with saturated $NaHCO_3$ (aq), extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated to give a yellow solid which was used without further purification. This material was dissolved in THF (300 ml) and treated with H_2O_2 (30%, 15 ml) at 0°C. The cooling bath was removed and the reaction mixture stirred for 0.5 h at room temperature. The mixture was quenched by adding NaOH (1 N, 300 ml). The mixture was extracted with CH_2Cl_2 (2 x 200 ml). The extracts were combined, dried ($MgSO_4$), concentrated, and purified by column chromatography (SiO_2 diethyl ether, Rf = 0.25) gave 2.7 g (60%) of **4.35** as colorless liquid. ^{1}H-NMR (200 MHz) δ = 6.42 (m, 1H), 5.84 (m, 1H), 3.34 (dt, *J* = 6 Hz, *J* = 1.0 Hz, 2H), 2.90 (d, *J* = 1.7 Hz, 3H), 2.33 (m, 2H); ^{13}C NMR (200 MHz) δ = 164.8, 139.0, 125.1, 47.3, 34.3, 23.8.

4.8 References

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